10/29/01

AN 91347256 MEDLINE
DN 91347256 PubMed ID: 1878890
TI Adriamycin(hydrazone)- ***antibody*** ***conjugates*** require ***internalization*** and intracellular acid hydrolysis for antitumor activity.
AU Braslawsky G R; Kadow K; Knipe J; McGoff K; Edson M; Kaneko T; Greenfield R S
CS Bristol-Myers Squibb, Wallingford, CT 06492-7600.
SO CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1991) 33 (6) 367-74.
Journal code: CN3; 8605732. ISSN: 0340-7004.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
ED Entered STN: 19911020
Last Updated on STN: 19970203
Entered Medline: 19911003
AB Adriamycin hydrazone (ADM-Hzn) immunoconjugates have previously been shown to exhibit antibody-directed antitumor activity in vitro and in vivo. In this report, the biological and biochemical properties of the mAb and linker were investigated. Conjugates prepared with two antibodies 5E9 [anti-(transferrin receptor)] and G28.1 (anti-CD37), (which internalize from the surface of target cells following binding) were more cytotoxic in vitro and had greater antitumor activity against Daudi B lymphoma tumor xenografts than a non-internalizing immunoconjugate prepared with mAb 2H7 (anti-CD20). In addition, the 13-acylhydrazone bond linking the drug to the mAb was labile at pH 5 and released unmodified ADM at a rapid rate (t1/2 = 2.5 h). Immunoconjugates prepared with an oxime linkage at the C-13 position were stable to acid and were not cytotoxic. These findings suggest that ***internalization*** of ADM-Hzn immunoconjugates and release of free ADM from the mAb in acidic intracellular compartments were important steps in the mechanism of action of ADM-Hzn immunoconjugates.

L4 ANSWER 65 OF 68 MEDLINE
AN 90304235 MEDLINE
DN 90304235 PubMed ID: 2364115
TI Cytotoxicity of glucose oxidase conjugated with antibodies to target cells: killing efficiency depends on the conjugate ***internalization***
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AU Muzykantov V R; Trubetskaya O V; Puchnina E A; Sakharov D V; Domogatsky S P
CS Institute of Experimental Cardiology, National Cardiology Research Center, Academy of Medical Sciences, Moscow, U.S.S.R.
SO BIOCHIMICA ET BIOPHYSICA ACTA, (1990 Jun 12) 1053 (1) 27-31.
Journal code: A0W; 0217513. ISSN: 0006-3002.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199008
ED Entered STN: 19900921
Last Updated on STN: 19900921
Entered Medline: 19900813
AB The cytotoxic action of glucose oxidase conjugated with antibodies against the target cells has been examined in a culture of human endothelial cells. Internalizable (anti-endothelial, MoAb E25) and non-internalizable (anti-fibronectin, MoAb FN) monoclonal antibodies were employed as vectors. Anti-endothelial monoclonal antibody E78 (whether it can be internalized by endothelial cells is unclear) and polyclonal mouse antiserum to the human endothelium were also used. The conjugates were prepared by oxidation of the enzyme carbohydrate moiety with periodate. Free conjugates display similar enzyme activity in glucose solution. In contrast to glucose oxidase, conjugated with no-immune IgG, ***antibody*** - ***conjugated*** glucose oxidase binds specifically to target cells. The efficiency of targeting was different for various conjugates. Targeting via the anti-fibronectin antibody and anti-endothelial antiserum provided maximal quantitative binding of glucose oxidase to endothelial cells, while the conjugates with MoAb E25 and MoAb E78 monoclonal antibodies provided less effective binding. In the presence of glucose, targeted glucose oxidase generated H2O2. Hydrogen peroxide is relatively stable in buffer, but rapidly decays in the culture medium supplemented with 20% human serum. Though the quantitative binding of MoAb E25-conjugated glucose oxidase was minimal comparing to other conjugates, targeting via MoAb E25 produced the maximal cytotoxic effect as well as targeting via polyclonal antiserum. The killing efficiencies of MoAb FN-conjugated and MoAb E78-conjugated glucose oxidase were about 30-fold lower. The high efficiency of the MoAb E25-conjugated enzyme may be due to its ***internalization*** by target cells.
Internalization can lead to unaccessibility of generated H2O2 for extracellular scavengers and pH optimization for glucose oxidase activity, which provides valuable advantages for the cytotoxicity of the conjugate. Thus, cytotoxicity of ***antibody*** - ***conjugated*** glucose oxidase depends not only on the efficiency of specific binding to the target cell, but also on the fate of cell-bound conjugate. Cytotoxicity is extremely effective in case of 'internalizable' conjugate and drastically less effective in case of 'non-internalizable' conjugate.

L4 ANSWER 59 OF 68 USPATFULL
AN 92:10860 USPATFULL
TI Cytotoxic drug conjugates and their delivery to tumor cells
IN Myers, Andre E., Genevea, Switzerland
Bichon, Daniel, Thorens-Glieres, France
PA Battelle Memorial Institute, Geneva, Switzerland (non-U.S. corporation)
PI US 5087616 19920211
AI US 1987-82244 19870806 (7)
PRAI EP 1986-810347 19860807
DT Utility
FS Granted
EXNAM Primary Examiner: Moezie, F. T.
LREP Cushman, Darby & Cushman
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 1012
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A therapeutic composition comprising a chemical conjugatge including a first moiety, other than an immunoglobulin or fragment thereof, such as epidermal growth factor, which preferentially binds to a tumor cell, and is internalized by the cell, and a second moiety linked to the first moiety, and comprising a biodegradable polymeric carrier, such as polyglutamic acid, to which one or more cytotoxic molecules, for instance, daunomycin, are attached. The degradation of the carrier by intracellular enzymes releases a cytotoxic agent, resulting in selective destruction of the tumor cells.

L4 ANSWER 52 OF 68 USPATFULL
AN 97:7681 USPATFULL
TI Bryodin 2 a ribosome-inactivating protein isolated from the plant Bryonia dioica
IN Siegall, Clay B., Edmonds, WA, United States
Gawlak, Susan L., Bellevue, WA, United States
Marquardt, Hans, Mercer Island, WA, United States
PA Bristol-Myers Squibb Company, New York, NY, United States (U.S. corporation)
PI US 5597569 19970128
AI US 1994-324301 19941020 (8)
RLI Continuation-in-part of Ser. No. US 1993-141891, filed on 25 Oct 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Chan, Christina Y.; Assistant Examiner: Gambel, Phillip
CLMN Number of Claims: 41
ECL Exemplary Claim: 1
DRWN 16 Drawing Figure(s); 16 Drawing Page(s)
LN.CNT 1876
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention discloses a new ribosome-inactivating protein, bryodin 2, isolated from the plant Bryonia dioica. This ribosome-inactivating protein (RIP) is a type IRIP having a single polypeptide chain and no cellular receptor domain. Like many type I RIPs, bryodin 2 has a molecular weight of about 27,000 daltons and a pI of 9.5. Bryodin 2 differs from previously identified ribosome-inactivating protein in its amino acid composition, amino acid sequence, and toxicity in vitro and in vivo. Bryodin 2 is useful, as are other type I ribosome-inactivating proteins, as an abortifacient, immunomodulator, anti-tumor or anti-viral agent. Compositions comprising bryodin 2 as an immunoconjugate or fusion molecule are particularly useful to kill cells of a target population.

L4 ANSWER 53 OF 68 MEDLINE
AN 1998068472 MEDLINE
DN 98068472 PubMed ID: 9404661
TI Generation and characterization of an anti-CD19 single-chain Fv immunotoxin composed of C-terminal disulfide-linked dgRTA.
AU Wang D; Li Q; Hudson W; Berven E; Uckun F; Kersey J H
CS University of Minnesota Cancer Center, Biotherapy Institute, Minneapolis 55455, USA.
NC CA 49721 (NCI)
SO BIOCONJUGATE CHEMISTRY, (1997 Nov-Dec) 8 (6) 878-84.
Journal code: A1T; 9010319. ISSN: 1043-1802.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199801
ED Entered STN: 19980206
Last Updated on STN: 19980206
Entered Medline: 19980127
AB Our laboratory utilized two methods to produce the anti-CD19 immunotoxin containing a single-chain Fv (scFv) FVS191 and a ricin A chain (RTA). The first method produced the recombinant protein FVS191CDRTA from a fusing

gene containing sequences encoding FVS191, catheptsin D proteinase digestion site (CD), and RTA. FVS191CDRTA did not show CD19 antigen binding and cytotoxic activity. The second method generated a disulfide-linked FVS191cys-dgRTA from a FVS191cys, the FVS191 with an additional C-terminal cysteine, and a deglycosylated RTA (dgRTA). The formation of FVS191cys-dgRTA is efficient; up to 70% of the proteins participating in the reaction had formed FVS191cys-dgRTA when the molar ratio of FVS191cys to dgRTA was 1:1. A competitive ELISA assay indicated that FVS191cys-dgRTA and the parental monoclonal antibody B43 possessed comparable CD19 binding abilities. The protein synthesis inhibition assay revealed that FVS191cys-dgRTA was toxic to CD19 positive cell lines, but it was less potent than the intact ***antibody*** - ***conjugated*** B43-dgRTA, which had an IC50 = 2 x 10(-11) M. 125I-Labeled FVS191 and 125I-labeled B43 were internalized by Nalm-6 cells at 37 degrees C as demonstrated by ***internalization*** studies; this result indicates that cross-linking of CD19 antigen is not required for the endocytosis of CD19 and raises the possibility that the lower cytotoxity of FVS191cys-dgRTA is not due to the monovalent binding of CD19 by FVS191cys-dgRTA. Our study with anti-CD19 scFv immunotoxin indicates that the formation of a disulfide-linked scFv immunotoxin is an alternative to the recombinant method of producing scFv immunotoxin.